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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,762	09/05/2003	Charles R. Cantor	701586-053023	6905
50607	7590	08/11/2008	EXAMINER	
RONALD I. EISENSTEIN 100 SUMMER STREET NIXON PEABODY LLP BOSTON, MA 02110				KIM, YOUNG J
ART UNIT		PAPER NUMBER		
1637				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/655,762	CANTOR ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 09 May 2008.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-3 and 10-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-3 and 10-13 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>5/9/2008</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 9, 2008 has been entered.

Preliminary Remark

Claims 4-9 and 14 have been canceled.

Claims 1-3 and 10-13 are pending and are under prosecution herein.

Information Disclosure Statement

The IDS received on May 9, 2008 is acknowledged and is being considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3 and 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref) in view of Amexis et

al. (PNAS, October 2001, vol. 98, no. 21, pages 12097-12102) and Ross et al. (BioTechniques, September 2000, vol. 29, pages 620-629)¹.

Becker et al. disclose a method of measuring the amount of target nucleic acid sequence in a biological sample, comprising the steps:

- a) preparing a sample by adding known amount of a standard nucleic acid, wherein said standard nucleic acid has a single nucleotide sequence difference from the target nucleic acid (page 9437, bottom paragraph, in the phrase, "mutated cDNA serves as internal standard"; and page 9438, 2nd paragraph; Figure 1);
- b) amplifying the sample of step (a) (see Figure 1, via PCR);
- c) using a further method to enhance the difference between the standard and the target nucleic acid sequence at the site resulting in enhanced products so that the difference created by the at least one base between the standard and the target nucleic acid can be detected (the digestion step of Figure 1 which enhances the difference between the standard and the target nucleic acid);
- d) quantifying the enhanced products of step (c) by measuring the ratio of the amplified target nucleic acid to the amplified standard nucleic acid to measure the amount of target nucleic acid present in the sample (Figure 2; page 9442, bottom paragraph).

The target nucleic acid is mRNA (page 9437, 2nd paragraph).

The enhancement is achieved via an enzyme which specifically cleaves at the site of differentiation (*Eco*RI digestion; page 9442, bottom paragraph).

Becker et al. do not employ mass spectrometry in their quantification method (claims 4 and 8).

¹ This rejection was already made in the Final Rejection mailed on November 21, 2007, wherein Ross et al. reference was cited as an evidentiary reference for Official Notice taken. The Final Rejection under this practice was justified as set

Becker et al. do not explicitly disclose a method of performing primer extension at the site of differentiation (claim 5), or allele-specific hybridization at the site of differentiation (claim 7).

Becker et al. do not explicitly disclose that the method measures the amount of at least 5, 10, 25, or 50 target nucleic acid sequences using at least 5, 10, 25, or 50 standard nucleic acids, respectively (claims 10-13).

Amexis et al. disclose a method of quantifying a target nucleic acid in a sample, in particular, RNA virus (thus infectious agent), wherein the method comprises the steps of:

- a) amplification of a target nucleic acid with a pair of primers (Figure 1B; page 12098, 2nd column, 3rd paragraph);
- b) amplifying the amplified product with MassExtend primers which is specific for a point mutation (Figure 1B; page 12098, 2nd column, 3rd paragraph (middle)); and
- c) detecting and quantifying the amplified products (Figure 1B; page 12098, 2nd column, 3rd paragraph (bottom); Abstract; page 12098, 1st column, 3rd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Becker et al. and with the teachings of Amexis et al., thereby arriving at the claimed invention for the following reasons.

The method employed by Becker et al., which is drawn to the amplifying the target nucleic acid and the standard nucleic acid (which contains a single nucleotide mutation) via use of primers which flank the target nucleic acid region, employs more than a decade old technique – that is – restriction digest, electrophoresis, followed by the radiolabeled (^{32}P) quantitation method.

Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to employ a non-radioactive method of accurately quantitating the target nucleic acid, such as MALDI-TOF, thereby arriving at the claimed invention.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings since methods of quantification employing mass spectrometry, such as SNuPE (single nucleotide primer extension), have been well-established.

For example, multiplex detection of different target nucleic acids (i.e., different markers) via MALDI-TOF was known prior to Applicants' filing of the application.

"A main advantage of MALDI-TOF MS-based genotyping is its ability to multiplex many primer extension assays within a single sample...Multiplex PCR and primer extension assays were performed for the CP450 polymorphism and a polymorphism in human LDLR region by amplifying homozygote and heterozygote samples. Multiplex PCR products from heterozygous mutant and homozygote samples were combined ... and the mixture was genotyped. The data show unambiguous detection of the low-abundance alleles for both loci tested. A quantitation study was not performed for the multiplex experiments; however, the data are presented here to provide a basis for future investigation." (page 625, Ross et al., "Quantitative Approach to Single-Nucleotide Polymorphism Analysis Using MALDI-TOF Mass Spectrometry," BioTechniques, September 2000, vol. 29, pages 620-629)

Given the fact that Amexis et al. amplify a known target nucleic acid sequence via use of a flanking primer pairs, followed by the mutation-specific primer extension, one of ordinary skill in the art would have recognized that the amplification products of Becker et al., would have served equally well for the mutation-specific primer extension, which would have been necessary for the subsequent mass spectrometric analysis.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants traverse the rejection.

Applicants state that the amended claims make explicit that the method is directed to an analysis of two genes not two alleles of the same gene. Accordingly, one has, in one reaction at least four different nucleic acid molecule populations, namely, one nucleic acid pair that corresponds to each gene and one standard which corresponds to each gene product but having one base pair difference in them (page 4, 4th paragraph, Response).

The examiner understands what Applicants are trying to indicate. However, it is respectfully submitted that this statement is not entirely accurate.

Claim 1, step a) states that a at least two target nucleic acids corresponding to the at least genes and a known amount of at least two standard nucleic acids, wherein said at least two standard nucleic acids have a nucleotide sequence that is one base different than the respective target nucleic acid.

In other words, each of the two target nucleic acids need not be double-stranded. Indeed, each of said targets could be single stranded. Similarly, the two standard nucleic acids need not be double-stranded.

In other words, a double-stranded nucleic acid having a single polymorphic mutation will meet the limitation of a first target nucleic acid and a first standard nucleic acid corresponding to said first target nucleic acid.

Similarly, a second double-stranded nucleic acid having a single polymorphic mutation will meet the limitation of a second target nucleic acid and a second standard nucleic acid corresponding to said second target nucleic acid.

However, even if one were to consider the Applicants' arguments, it is respectfully pointed out that the claims are deemed obvious.

As Ross et al. pointed out, the main advantage of MALDI-TOF MS-based genotyping is its ability to multiplex many primer extension assays within a single sample (see above for citation page). Ross et al. even point out that the multiplex PCR and primer extension assays were performed for the CP450 polymorphism and a polymorphism in human LDLR region by amplifying homozygote and heterozygote samples.

Clearly, these are multiplex amplification of two different genes.

Based on the teachings already provided for by Becker et al. and Amexis et al., one of ordinary skill in the art would have been clearly motivated to employ the MALDI-TOF, thereby arriving at the claimed invention. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at multiplexing given the fact that Ross et al. disclose that MALDI-TOF method allowed them to multiplex many primer extensions assays within a single sample, wherein the artisans explicitly demonstrated the multiplexing of two different target nucleic acids of different genes.

With regard to Applicants' arguments drawn to the quantitation not being taught by the references of record (page 4, bottom paragraph to page 5, 1st paragraph, Response), it is respectfully submitted that Ross et al. state the following:

"A quantitation study was not performed for the multiplex experiments; however, the data are presented here to provide a basis for future investigation." (page 625, Ross et al.)

For this aspect, it is respectfully submitted that in KSR (citation omitted), the court stated:

"A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under 103." (from KSR International Co. v. Teleflex Inc. 82 USPQ2d 1385 (2007, Supreme Court) at 1397).

Therefore the invention as claimed is deemed *prima facie* obvious over the cited references and the rejection is maintained for the reasons already of record.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and 10-13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/589,709. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are conflicting in the subject matter in that both inventions employ the use of a standard (or competitor) which has a different sequence than the sequence of the target nucleic acid for the purpose of quantifying, wherein the application clearly contemplates mass spectrometry.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

Art Unit: 1637

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
8/11/2008

/YJK/